



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/852,976	05/10/2001	Tse W. Chang	THI-001	4934

959 7590 02/26/2003

LAHIVE & COCKFIELD
28 STATE STREET
BOSTON, MA 02109

EXAMINER

HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
----------	--------------

1644

DATE MAILED: 02/26/2003

15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/852,976	CHANG ET AL.	
	Examiner	Art Unit	
	" Neon" Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE Three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 1/8/02; 12/10/02.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-59 is/are pending in the application.
- 4a) Of the above claim(s) 7-10, 22-24, 33 and 41-59 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6, 11-21, 25-32 and 34-40 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 10 May 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>9</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 1-59 are pending.
2. Applicant's election with traverse of Group I, Claims 1-5, 7, 9, 11-23, 25-32 and 34-40 (now claims 1-6, 11-21, 25-32, and 34-40) drawn to an immunogenic composition comprising a first polypeptide coupled to a second polypeptide wherein the second polypeptide is heterologous to a subject that read on the species of CD79 α (Ig α) for the first polypeptide and IgG Fc for the second polypeptide, filed 12/10/02, is acknowledged. The traversal is on the grounds that (1) Groups I, II, III, IV and V should be reformed as group I because claim 1 embraces the species of cell-associated or soluble antigen, a cell surface receptor, a cytokine, a hormone and a tumor cell antigen. (2) Group VII, VIII, IX, X, XI and XII should be reformed as a single containing claims 44-59. This is not found persuasive because of the reasons set forth in the restriction mailed 6/4/02. However, the prior art search has been extended to include CD79 β and Ig since they are part of the B cell receptor. It is a burden to search more than one invention. Therefore, the requirement of Group I (now claims 1-6, 11-17, 19-21, 25-28, 31-36, 38-40) and Groups II-XII is still deemed proper and is therefore made FINAL.
3. Claims 7-10, 22-24, 33 and 41-59 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.
4. Claims 1-6, 11-21, 25-32, and 34-40 drawn to an immunogenic composition comprising a first polypeptide coupled to a second polypeptide wherein the first autologous polypeptide to a subject that read on the species of CD79 α (Ig α), CD79 β and Ig and wherein the second heterologous polypeptide that read on IgG Fc are being acted upon in this Office Action.
5. The disclosure is objected to because of the following informalities: (1) "is can be used" on page 11 at lines 21-22 which should have been "can be used" (2) incorporation of subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP 608.01(p), paragraph I regarding incorporation by reference. Therefore the embedded hyperlink and/or other form of browser-executable code disclosed on pages 19, at line 28 of the instant specification is

Art Unit: 1644

impermissible and require deletion. Where the hyperlinks and/or other forms of browser-executable codes are part of applicant's invention and are necessary to be included in the patent application in order to comply with the requirements of 35 U.S.C. 112, first paragraph, and applicant does not intend to have these hyperlinks be active links, then this objection will be withdrawn and the Office will disable these hyperlinks when preparing the patent text to be loaded onto the PTO web database and (3) "100 ml" on page 18 is a typographical error because it is physiologically impossible to collect 100 ml of blood from each immunized mouse. It should be "100 μ l". Appropriate action is required.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-6, 11-21, 25-32, and 34-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an immunogenic composition comprising a first polypeptide coupled to a second polypeptide, wherein the first polypeptide selected from the group consisting of CD79 α , CD79 β , and CD20, the second polypeptide is the Fc fragment of Ig heterologous to a subject, and the composition being capable of eliciting an immune response against the an autologous antigen in the subject, (2) the said composition wherein the autologous antigen is a cell-associated antigen, a cell surface receptor, is expressed by a B cell, (3) the said composition wherein the autologous antigen is expressed specifically by activated B cells, (4) the said composition wherein the first polypeptide and the second polypeptide are expressed as a fusion protein, (5) The said composition wherein the first fusion protein is dimeric, (6) The said composition wherein the first polypeptide and the second polypeptide are coupled via a chemical linkage, (7) the said composition wherein the second polypeptide consisting of at least the Fc region of an immunoglobulin molecule, (8) A composition comprising a first polypeptide which is autologous to a human subject coupled to a second polypeptide which is heterologous to the human subject, wherein the first polypeptide selected from the group consisting of CD79 α , CD79 β , and CD20, the second polypeptide is the Fc fragment of an immunoglobulin heterologous to a subject, and the composition being capable of eliciting an immune response against the an autologous antigen in the subject, (9) the said composition comprising a first polypeptide which is autologous to a human subject coupled to a second polypeptide which is

Art Unit: 1644

second polypeptide which is heterologous to the human subject wherein the autologous antigen is a cell-associated antigen, and expressed by a B cell, (10) the said composition comprising a first polypeptide which is autologous to a human subject coupled to a second polypeptide which is heterologous to the human subject wherein the first polypeptide and the second polypeptide are expressed as a fusion protein, or the fusion protein is dimeric or the first polypeptide and the second polypeptide are coupled via a chemical linkage, (11) the said composition comprising a first polypeptide which is autologous to a human subject coupled to a second polypeptide which is heterologous to the human subject wherein the second polypeptide consisting of at least the Fc region of an immunoglobulin molecule, (12) A composition for targeting B cells in a subject comprising a first polypeptide which is autologous to the subject, coupled to a second polypeptide, which is heterologous to the subject wherein the first polypeptide consisting of an immunogenic portion of polypeptide expressed by a B cell in the subject wherein the first polypeptide is selected from the group consisting of CD79 α , CD79 β , and CD20 and the second polypeptide consisting of the Fc portion of the immunoglobulin, (13) the said composition for targeting B cells in a subject wherein the autologous antigen is a cell-associated antigen, (14) the said composition for targeting B cells in a subject wherein the first polypeptide and the second polypeptide are expressed as a fusion protein, and (15) the said composition for targeting B cells in a subject wherein the first polypeptide and the second polypeptide are expressed as a fusion protein wherein the fusion protein is dimeric for eliciting autoantibodies against the autologous antigen expressed on the B cell of the subject, does not reasonably provide enablement for (1) *any* immunogenic composition comprising *any* "first polypeptide" coupled to *any* "second polypeptide" wherein the second polypeptide is heterologous to a subject, the composition being capable of eliciting any immune response against *any* autologous antigen in the subject, (2) *any* immunogenic composition, comprising *any* "first polypeptide", wherein the first polypeptide is sufficiently "homologous" to *any* "autologous polypeptide" in a subject, coupled to *any* second polypeptide, wherein the second polypeptide is heterologous to the subject, the composition being capable of eliciting any immune response against any autologous antigen in the subject, (3) *any* immunogenic composition, comprising *any* "first polypeptide" which is autologous to a subject, coupled to *any* "second polypeptide", which is heterologous to the subject, the composition being capable of eliciting any immune response against *any* "autologous antigen", any "autologous antigen" in the subject such as the ones recited in claim 9, (4) *any* immunogenic composition mentioned above wherein the subject is a human, (5) *any* immunogenic composition mentioned

above wherein the autologous antigen is *any* "cell-associated antigen", *any* "cell surface receptor", *any* "autologous antigen" is expressed by a B cell or B cells, *any* "autologous antigen is expressed specifically by activated B cells", (6) *any* immunogenic composition, comprising *any* "first polypeptide" which is autologous to a subject, coupled to *any* "second polypeptide", which is heterologous to the subject, the composition being capable of eliciting any immune response against *any* autologous antigen targeted for reduction or elimination, (7) the said immunogenic composition wherein the autoantigen is any cell-associated antigen, *any* autologous antigen such as the ones recited in claim 23, any soluble antigen, any autologous antigen is expressed by a B cell, (8) the said immunogenic composition wherein the first polypeptide and the second polypeptide are expressed as a fusion protein, or a dimeric fusion protein, (9) the said composition wherein the second polypeptide "comprises" at least "a portion" of an Fc region of an immunoglobulin molecule, (10) *any* composition for targeting B cells in a subject comprising any "first polypeptide", which is autologous to the subject, coupled to any "second polypeptide", which is heterologous to the subject, wherein the first polypeptide "comprises" any immunogenic portion of any polypeptide expressed by a B cell in a subject and wherein the composition is capable of eliciting an immune response to any autologous B cell antigen in the subject, (11) the said composition for targeting B cells wherein the autologous antigen is *any* "cell-associated antigen", (12)) the said composition for targeting B cells wherein the first polypeptide and the second polypeptide are expressed as a fusion protein, or the fusion protein is dimeric, (13) the said composition for targeting B cells wherein the second polypeptide "comprises" at least one helper cell epitope, (14) the said composition for targeting B cells wherein the second polypeptide "comprises" at least any "portion" of an Fc region of an immunogenic molecule, (14) *any* composition comprising *any* "human polypeptide" coupled to *any* polypeptide comprising at least *any* portion of *any* "non-human immunoglobulin molecule", and (15) *any* composition comprising *any* "human polypeptide" coupled to *any* polypeptide comprising at least *any* portion of *any* "non-human immunoglobulin molecule" wherein the portion of the non-human immunoglobulin molecule is derived from the Fc portion of the immunoglobulin wherein the composition being capable of eliciting any immune response against any autologous antigen in the subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only four fusion proteins selected from the group consisting of (1) mouse Ig β fused to human IgG Fc, (2) CD79 α fused to the Fc region of IgG1 and (3) CD79 β fused to fused to the Fc region of IgG1 and mouse CD20 fused to human IgG Fc for making autoantibody to the Ig β , CD79 α , CD79 β and CD20 expressed by B cell, respectively.

The specification does not teach how to make and use *any* immunogenic composition comprising any "first polypeptide coupled to or fused to any "second polypeptide" heterologous to the subject because the terms "first polypeptide", "second polypeptide" and "autologous antigen" without SEQ ID NO: do not convey any structure such as the amino acid sequence, much less about the function.

Stryer *et al* teach a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence and the corresponding nucleic acid sequence determines the conformational of the protein (See enclosed relevant pages). Given the indefinite number of "first polypeptide", "second polypeptide" and "autologous antigen", there are insufficient guidance as to the structure, the amino acid sequence of any "first polypeptide", "second polypeptide" and "autologous antigen". Further, there are insufficient working examples demonstrating that any immunogenic composition comprising any undisclosed "first polypeptide", "second polypeptide" and "autologous antigen" is effective for eliciting autoantibodies response against any "autologous antigen" in the subject. In the absence of guidance as to the structure of the "first polypeptide", "second polypeptide" and "autologous antigen", it is unpredictable which undisclosed "first polypeptide", "second polypeptide" and "autologous antigen" would be useful and effective as a pharmaceutical composition for treating any disease by stimulating autoantibodies immune response. Not only said "autologous polypeptide" has no structure, there is insufficient guidance as how to determine the first polypeptide "sufficiently homologous" the undisclosed "autologous polypeptide".

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo *et al.*, 1994, *The Protein Folding Problem and Tertiary Structure Prediction*, pp. 492-495). Without the specific guidance as to which amino acid within the full-length of any autologous polypeptide can be deleted, substitute, and whether the resulting polypeptide maintained the same structure and function as the "autologous polypeptide", it would take undue amount experimentation even for one skill in the art to practice the claimed invention.

Likewise, there is insufficient guidance as to the structure associated with the term "cell-associated antigen", "cell surface receptor", and "autologous antigen" expressed by B cells or activated B cells, much less having any function associated with "cell-associated antigen", "cell surface receptor", and "autologous antigen" expressed by B cells or activated B cells. Since the immunogenic composition comprising the "first polypeptide" and the "second polypeptide" is not enabled, it follows that any composition comprising a "first polypeptide" and a "second polypeptide" wherein the "first polypeptide" and "second polypeptide" are expressed as a fusion protein, or coupled via a chemical linkage or a dimeric fusion protein are not enabled. It also follows that any composition comprising any undisclosed second polypeptide comprises at least one T helper cell epitope is not enabled. With regard to claim 19, the term "comprises" is open-ended. It expands the second polypeptide to include additional amino acid residues at either or both ends of any "portion" of any undisclosed "second polypeptide". There is insufficient guidance as to the undisclosed amino acid residues to be added and whether the resulting fusion protein in the immunogenic composition has the same function as the fusion protein without the extra undisclosed amino acid residues. Further, the term "portion" could be as little as one amino acid of an Fc immunoglobulin. There is insufficient guidance as to the structure of any first polypeptide fused to any "second polypeptide" wherein the "second polypeptide" could be any portion of an Fc region or could be as little as one amino acid, in turn, would be effective for eliciting an autoantibodies immune response to any autologous antigen targeted for reduction or elimination of B cell for treating any disease.

Kuby *et al* teach that immunizing a peptide comprising a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in antibody specificity that differs from antibody specificity directed against the native full-length polypeptide. Given the indefinite number of undisclosed amino acids that can be added, it is

Art Unit: 1644

unpredictable which undisclosed polypeptide would be useful for any purpose, especially for generating autoantibodies against a specific autoantigen to eliminate B cells in vivo.

Colman *et al* teach that even a single amino acid changes within the interface of an antibody-antigen can raise or lower the affinity of the antibody (See page 33, in particular).

Even if the "first polypeptide" is limited to the specific first polypeptide to mouse Ig β , CD79 α , CD79 β and CD20 expressed by B cell, and the "second polypeptide" is limited to the human Fc fragment of immunoglobulin, the immune response such as antibody generate from immunizing the fusion protein mentioned above would be specific for antigen such as Ig β , CD79 α , CD79 β and CD20 expressed by B cell. There is insufficient guidance and working example that the claimed immunogenic composition is effective for inducing autoantibody immune response against *any* "autologous antigen" when immunized only with Ig β -Fc, CD79 α -Fc, CD79 β -Fc and CD20-Fc fusion protein.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of *Ex parte Aggarwal*, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

8. Claims 1-6, 11-21, 25-32, and 34-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* immunogenic composition comprising *any* "first polypeptide" coupled to *any* "second polypeptide" wherein the second polypeptide is heterologous to a subject, the composition being capable of eliciting any immune response against *any* autologous antigen in the subject, (2) *any* immunogenic composition, comprising *any* "first polypeptide", wherein the first polypeptide is sufficiently "homologous" to *any* "autologous polypeptide" in a subject, coupled to *any* second polypeptide, wherein the second polypeptide is heterologous to the subject, the composition being

Art Unit: 1644

capable of eliciting any immune response against any autologous antigen in the subject, (3) *any* immunogenic composition, comprising *any* "first polypeptide" which is autologous to a subject, coupled to *any* "second polypeptide", which is heterologous to the subject, the composition being capable of eliciting any immune response against *any* "autologous antigen", any "autologous antigen" in the subject such as the ones recited in claim 9, (4) *any* immunogenic composition mentioned above wherein the subject is a human, (5) *any* immunogenic composition mentioned above wherein the autologous antigen is *any* "cell-associated antigen", *any* "cell surface receptor", *any* "autologous antigen" is expressed by a B cell or B cells, *any* "autologous antigen is expressed specifically by activated B cells", (6) *any* immunogenic composition, comprising *any* "first polypeptide" which is autologous to a subject, coupled to *any* "second polypeptide", which is heterologous to the subject, the composition being capable of eliciting any immune response against *any* autologous antigen targeted for reduction or elimination, (7) the said immunogenic composition wherein the autoantigen is any cell-associated antigen, *any* autologous antigen such as the ones recited in claim 23, any soluble antigen, any autologous antigen is expressed by a B cell, (8) the said immunogenic composition wherein the first polypeptide and the second polypeptide are expressed as a fusion protein, or a dimeric fusion protein, (9) the said composition wherein the second polypeptide "comprises" at least "a portion" of an Fc region of an immunoglobulin molecule, (10) *any* composition for targeting B cells in a subject comprising any "first polypeptide", which is autologous to the subject, coupled to any "second polypeptide", which is heterologous to the subject, wherein the first polypeptide "comprises" any immunogenic portion of any polypeptide expressed by a B cell in a subject and wherein the composition is capable of eliciting an immune response to any autologous B cell antigen in the subject, (11) the said composition for targeting B cells wherein the autologous antigen is *any* "cell-associated antigen", (12)) the said composition for targeting B cells wherein the first polypeptide and the second polypeptide are expressed as a fusion protein, or the fusion protein is dimeric, (13) the said composition for targeting B cells wherein the second polypeptide "comprises" at least one helper cell epitope, (14) the said composition for targeting B cells wherein the second polypeptide "comprises" at least any "portion" of an Fc region of an immunogenic molecule, (14) *any* composition comprising *any* "human polypeptide" coupled to *any* polypeptide comprising at least *any* portion of *any* "non-human immunoglobulin molecule", and (15) *any* composition comprising *any* "human polypeptide" coupled to *any* polypeptide comprising at least *any* portion of *any* "non-human immunoglobulin molecule" wherein the portion of the non-human

Art Unit: 1644

immunoglobulin molecule is derived from the Fc portion of the immunoglobulin wherein the composition being capable of eliciting any immune response against any autologous antigen in the subject.

The specification does not teach how to make and use *any* immunogenic composition comprising *any* "first polypeptide coupled to or fused to *any* "second polypeptide" heterologous to the subject because the terms "first polypeptide", "second polypeptide" and "autologous antigen" without SEQ ID NO: do not convey any structure such as the amino acid sequence, much less about the function of said first and second polypeptides, as well as autologous antigen.

With the exception of the specific immunogenic composition comprising the specific polypeptide mentioned above fused to the specific second polypeptide, there is inadequate written description about the structure associated with function of *any* immunogenic composition mentioned above comprising *any* "first polypeptide" coupled to or fused to *any* "second polypeptide" heterologous to the subject, *any* "autologous polypeptide", *any* "autologous antigen", *any* "cell-associated antigen", *any* "cell surface receptor", *any* "autologous antigen" expressed by a B cell or B cells or activated B cells, because said "first polypeptide", "second polypeptide", "autologous antigen" *any* "cell-associated antigen", and *any* "cell surface receptor" without SEQ ID NO (i.e. amino acid sequence) lack structure (i.e. amino acid sequence), much less about the function. Since the immunogenic composition comprising the "first polypeptide" and the "second polypeptide" is not adequately described, it follows that any composition comprising a "first polypeptide" and a "second polypeptide" wherein the "first polypeptide" and "second polypeptide" are expressed as a fusion protein, or coupled via a chemical linkage or a dimeric fusion protein are not adequately described. It also follows that any composition comprising any undisclosed second polypeptide comprises at least one T helper cell epitope is not adequately described. With regard to claim 19, the term "comprises" is open-ended. It expands the second polypeptide to include additional amino acid residues at either or both ends of a portion of any undisclosed "second polypeptide". There is insufficient written description about the additional undisclosed amino acids to be added, let alone having any functions, in turn, for inducing an immune response such as autoantibodies. Further, the term "portion" could be as little as one amino acid of an Fc immunoglobulin. There is insufficient written description about the structure of the portion of any Fc immunoglobulin since the "portion" could be as little as one amino acid, in turn, would be effective for eliciting an autoantibodies immune response to any autologous antigen targeted for reduction or elimination of B cell for treating any disease.

Art Unit: 1644

The specification discloses only Ig from human and mouse Ig β , CD79 α , CD79 β and CD20 expressed by B cell, given the lack of a written description of *any* additional representative species of "first polypeptide", "second polypeptide", "autologous polypeptide", "autologous antigen", "cell-associated antigen", "cell surface receptor", "Fc portion of any immunoglobulin", and *any* "immunogenic portion of any polypeptide expressed by any B cell in a subject", one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-4, 14, 16, and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,837,268 (Nov 1998; PTO 892).

The '268 patent teaches an immunogenic composition comprising a first polypeptide such as autologous polypeptide (self) GnRH coupled to or fused to a second polypeptide such as heterologous polypeptide (non-self) leukotoxin to the subject wherein the reference second polypeptide in the composition is capable of eliciting and enhancing the immune response such as antibody against the reference autologous (endogenous or self) antigen GnRH (See abstract, column 15, lines 51-53, column 21 at line 45, column 22, lines 61-65, column 11, lines 53-59, in particular). The '268 patent further teaches homologous GnRH polypeptide to the autologous GnRH in the reference immunogenic composition (See column 6, lines 7-12, in particular). The reference composition wherein the reference first polypeptide such as GnRH and the reference second polypeptide such as Leukotoxin are coupled via a chemical linkage that are known to those skilled in the art (See column 15, lines 36-41, in particular). The reference composition wherein the reference second polypeptide leukotoxin includes a spacer sequence that provides an

Art Unit: 1644

immunogenic helper T cell epitopes (See column 12, lines 60-67, in particular). Thus, the reference teachings anticipate the claimed invention.

11. Claims 1-4, 14, 19 and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Nissim *et al* (EMBO J 10(1): 101-107, 1991; PTO 892).

Nissim *et al* teach an immunogenic composition comprising a first autologous polypeptide such as a self mouse IgE CH3 domain or homolog thereof such as CHM3 coupled to a second heterologous polypeptide such as a portion of human IgE Fc region CH1, CH2 and CH4 domains of an immunoglobulin molecule (See page 102, chimeric human-mouse IgE, Fig 1, page 103, column 1, first full paragraph, in particular) in cell culture medium (see page 107, Immunoassays and binding assays for IgE, in particular). The reference composition wherein the reference human-mouse chimeric IgE is inherently capable of eliciting an immune response such as antibody against the self and non-self IgE in the subject (See Fig 2, in particular). Claim 4 is included in this rejection because the reference composition is for treating allergy in human subject. Thus, the reference teachings anticipate the claimed invention.

12. Claims 1-4, 14, 18-19, 37 and 39-40 are rejected 35 U.S.C. 102(b) as being anticipated by US Pat NO. 5,653,980 (Aug 1997; PTO 892).

The '980 patent teaches an immunogenic composition comprising a first polypeptide such as the CH1 domain of IgE from mammalian species such as human and rat fused to a second polypeptide such as the entire sequence or part thereof of the constant CH2-CH3 domains of IgE that lacks the CH1 domain from mammalian species such as human and rat and wherein the reference IgE domains are mutually exchange (self versus non-self) and further fused to glutathione-S-transferase (Sj26) from *S japonicum* which is a T helper epitope (See column 4, lines 21-26, column 9, lines 22-26, in particular). The reference composition has the ability to induce an immune response such as against self IgE (See column 4, lines 63-64, column 10, example 2, in particular). The term "comprising" is open-ended. It expands the claimed polypeptide to include additional amino acids at either or both ends to read on the reference fusion polypeptide. The '980 patent further teaches that by coupling of one's own CH2-CH3 region to a non-species specific protein, one can circumvent tolerance to self IgE and give help to B-cells producing antibodies against a species specific antibodies (See column 5, lines 16-25, in particular). Thus, the reference teachings anticipate the claimed invention.

Art Unit: 1644

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

14. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(c), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 3, 5-6, 11-15 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nissim *et al* (EMBO J 10(1): 101-107, 1991; PTO 892) or US Pat NO. 5,653,980 (Aug 1997; PTO 892) each in view of Hashimoto *et al* (Immunogenetics 40: 287-295, 1994; PTO 892) or Kooten *et al* (Clin Exp Immunol 110: 509-515, 1997; PTO 892).

The teachings of Nissim *et al* and the '980 patent have been discussed supra.

The claimed invention as recited in claim 5 differs from the teachings of the references only that the autologous antigen is a cell-associated antigen.

The claimed invention as recited in claim 6 differs from the teachings of the references only that the autologous antigen is a cell surface receptor.

The claimed invention as recited in claims 11-13 differs from the teachings of the references only that the autologous antigen is expressed by a B cell.

The claimed invention as recited in claim 15 differs from the teachings of the references only that the composition wherein the fusion protein is dimeric.

The claimed invention as recited in claim 17 differs from the teachings of the references only that the first polypeptide comprises at least a portion of a molecule selected from the group consisting of CD79 α , CD79 β and Ig.

Hashimoto *et al* teach a polypeptide such as human and mouse CD79 α (Ig- α /mb-1) that is a B cell-associated antigen that forms heterodimer with CD79 β to become a B cell surface

Art Unit: 1644

receptor (See page 287, column 2, page 288, Figures 1&2, in particular). The reference polypeptide human CD79 α (Ig- α /mb-1) forming complex with CD79 β is critical for both cell surface expression and signaling functions of the B cell receptor (BCR) (See page 287, column 2, in particular).

Kooten *et al* teach that CD79 α (Ig- α /mb-1) and Ig- β (B29 or CD79 β) together form the B cell receptor and play a critical role in the development of B cells (See page 509, column 1, first paragraph, in particular). Kooten *et al* teach that that the same receptor can be used for negative selection processes to eliminate B cells with specificity for autoantigens (See page 510, column 1, first paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the mouse IgE as taught by Nissim *et al* or the IgE molecule as taught by the '980 patent for the CD79 α (Ig- α /mb-1) as taught by Hashimoto *et al* or the Ig- β (B29 or CD79 β) as taught by Kooten *et al* for an immunogenic composition comprising a first polypeptide which is a mouse CD79 α or CD79 β coupled to a second polypeptide such as the Fc region CH1, CH2 and CH4 domains of an immunoglobulin molecule such as human IgE as taught by Nissim *et al*, the '980 patent, Hashimoto *et al* and Kooten *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Hashimoto *et al* teach human CD79 α (Ig- α /mb-1) forming complex with CD79 β is critical for both cell surface expression and signaling functions of the B cell receptor (BCR) (See page 287, column 2, in particular). The '980 patent teaches that domain swapping such as human IgE for rat or IgE and by coupling of one's own protein to a non-species specific protein, one can circumvent induction of tolerance to self IgE and give help to B-cells producing antibodies against a species specific antibodies (See column 5, lines 16-25, in particular). Kooten *et al* teach that that the CD79 α (Ig- α /mb-1) and Ig- β (B29 or CD79 β) B cell receptor can be used for negative selection processes to eliminate B cells with specificity for autoantigens (See page 510, column 1, first paragraph, in particular). Nissim *et al* teach a self-polypeptide coupled to a non-self polypeptide could form an immunogenic composition (See page 102, chimeric human-mouse IgE, Fig 1, page 103, column 1, first full paragraph, in particular). Claim 15 is included in this rejection because it is an inherent property that the reference Fc molecule that is capable of

Art Unit: 1644

dimerizing since it contains a cysteine residue at 328 in the Fc region, which is responsible for interchain disulfide bond.

16. Claims 3, 16 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nissim *et al* (EMBO J 10(1): 101-107, 1991; PTO 892) or US Pat NO. 5,653,980 (Aug 1997; PTO 892) each in view of US Pat 5,225,538 (July 1993; PTO 892).

The teachings of Nissim *et al* and the '980 patent have been discussed supra.

The claimed invention as recited in claim 16 differs from the teachings of the references only that the composition wherein the first and second polypeptides are coupled via a chemical linkage.

The claimed invention as recited in claim 19 differs from the teachings of the references only that the composition wherein the second polypeptide comprises at least a portion of an Fc region of an immunoglobulin molecule.

The '538 patent teaches a composition comprising a first polypeptide such as mouse LHR fused to (See column 15, line 32, in particular) or chemically crosslinks with crosslinking agent such as hydroxysuccinimide ester (See column 21, lines 49-61, in particular) to the Fc portion such as the CH2 and CH3 domains of human immunoglobulin such as IgG-1, IgG2, IgG3 or IgG4 (See column 10, lines 20-24, column 14, lines 40-41, column 46, line 35, in particular). The '538 patent teaches the Fc fusion protein improves the in vivo half of the reference fusion molecule (See column 14, lines 66-67, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the human IgE Fc region CH1, CH2 and CH4 domains of an immunoglobulin molecule as taught by Nissim *et al* for the Fc portion such as the CH2 and CH3 domains of human immunoglobulin such as IgG-1, IgG2, IgG3 or IgG4 as taught by the '538 patent or fusing the IgE as taught by the '980 to the Fc portion such as the CH2 and CH3 domains of human immunoglobulin such as IgG-1, IgG2, IgG3 or IgG4 as taught by the '538 patent for an immunogenic composition comprising a first polypeptide which is a mouse IgE or rat IgE coupled to a second polypeptide such as the human CH2 and CH3 domains of IgG-1, IgG2, IgG3 or IgG4 as taught by Nissim *et al*, the '980 patent and the '538 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Art Unit: 1644

One having ordinary skill in the art would have been motivated to do this because the '538 patent teaches the Fc fusion protein improves the in vivo half of the reference fusion molecule (See column 14, lines 66-67, in particular).

17. Claims 20-21, 25-32 and 34-36, 38 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,925,351 (July 1999, PTO 892) in view of Hashimoto *et al* (Immunogenetics 40: 287-295, 1994; PTO 892) or Kooten *et al* (Clin Exp Immunol 110: 509-515, 1997; PTO 892) and US Pat NO. 5,653,980 (Aug 1997; PTO 892).

The '351 patent teaches an immunogenic composition comprising a first polypeptide such as human or mouse lymphotoxin- β receptor fused to a second polypeptide such as the Fc domain of IgG4 immunoglobulin that are ineffective at activating complement that leads to reduction or elimination of the reference fusion protein. The '351 patent further teaches that one can select a Fc domain based on whether its associated secondary effector functions are desirable for particular immune response or disease being treated with the fusion protein (See column 12, line 63-65, in particular) and soluble receptor that function as a blocking agent is useful for treating lymphocyte mediated immunologically disease (See abstract, in particular).

The claimed invention as recited in claim 20 differs from the teachings of the reference only that the composition comprising a first polypeptide which is autologous to a human subject coupled to a second polypeptide which is heterologous to the human subject, wherein the composition is capable of eliciting an immune response to an autologous antigen targeted for reduction or elimination.

The claimed invention as recited in claims 21 and 32 differs from the teachings of the reference only that the autologous antigen is a cell-associated antigen.

The claimed invention as recited in claims 25 differs from the teachings of the reference only that the autologous antigen is expressed by a B cell.

The claimed invention as recited in claims 27 and 35 differs from the teachings of the reference only that the composition wherein the fusion protein is dimeric.

The claimed invention as recited in claims 28 and 36 differs from the teachings of the reference only that the first polypeptide comprises at least a portion of a molecule selected from the group consisting of CD79 α , CD79 β and Ig.

The claimed invention as recited in claims 29, 38 and 40 differs from the teachings of the reference only that the second polypeptide comprises at least a portion of an Fc region of an immunoglobulin molecule.

The claimed invention as recited in claim 30 differs from the teachings of the reference only that the composition wherein second polypeptide comprises at least a portion of an immunoglobulin molecule.

The claimed invention as recited in claim 31 differs from the teachings of the reference only that a composition for targeting B cells in a subject comprising a first polypeptide, which is autologous to the subject, coupled to a second polypeptide, which is heterologous to the subject, coupled to a second polypeptide, which is heterologous to the subject, wherein the first polypeptide comprises an immunogenic portion of a polypeptide expressed by a B cell in the subject and wherein the composition is capable of eliciting an immune response to an autologous B cell antigen in the subject.

Hashimoto *et al* teach a polypeptide such as human and mouse CD79 α (Ig- α /mb-1) that is a B cell-associated antigen that forms heterodimer with CD79 β to become a B cell surface receptor (See page 287, column 2, page 288, Figures 1&2, in particular). The reference polypeptide human CD79 α (Ig- α /mb-1) forming complex with CD79 β is critical for both cell surface expression and signaling functions of the B cell receptor (BCR) (See page 287, column 2, in particular).

Kooten *et al* teach that CD79 α (Ig- α /mb-1) and Ig- β (B29 or CD79 β) together forming the B cell receptor and play a critical role in the development of B cells (See page 509, column 1, first paragraph, in particular). Kooten *et al* teach that that the same receptor can be used for negative selection processes to eliminate B cells with specificity for autoantigens (See page 510, column 1, first paragraph, in particular).

The '980 patent teaches an immunogenic composition comprising a first polypeptide such as the CH1 domain of IgE from mammalian species such as human and rat fused to a second polypeptide such as the entire sequence or part thereof of the constant CH2-CH3 domains of IgE that lacks the CH1 domain from mammalian species such as human and rat and wherein the reference IgE domains are mutually exchange (self versus non-self) and wherein the reference fusion polypeptide further fuses to glutathione-S-transferase (Sj26) from *S japonicum* which is a T helper epitope (See column 4, lines 21-26, column 9, lines 22-26, in particular). The reference composition has the ability to induce an immune response such as against the body's own IgE

Art Unit: 1644

(See column 4, lines 63-64, column 10, example 2, in particular). The term "comprising" is open-ended. It expands the claimed polypeptide to include additional amino acids at either or both ends to read on the reference fusion polypeptide. The '980 patent further teaches that by coupling of one's own CH2-CH3 region to a non-species specific protein, one can circumvent tolerance to self IgE and give help to B-cells producing antibodies against a species specific antibodies (See column 5, lines 16-25, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the human lymphotoxin- β receptor portion of the fusion protein as taught by the '351 patent for the human or mouse CD79 α (Ig- α /mb-1) as taught by Hashimoto *et al* or the human Ig- β (B29 or CD79 β) as taught by Kooten *et al* fused to the Fc region of human or mouse immunoglobulin molecule such as IgG4 as taught by the '351 *et al* further comprising the T helper cell epitope as taught by the '980 patent for an immunogenic composition that is capable of eliciting an immune response such as antibody production to an autologous B cell antigen targeted for reduction or elimination as taught by the '351 patent, Hashimoto *et al*, Kooten *et al* and the '980 patent. Alternatively, the human or mouse CD79 α (Ig- α /mb-1) as taught by Hashimoto *et al* or the human Ig- β (B29 or CD79 β) as taught by Kooten *et al* is coupled to the Fc portion such as CH2 CH3 domains of an immunoglobulin such as IgE from rat as taught by the '980 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '351 patent teaches that one can select a Fc domain based on whether its associated secondary effector functions are desirable for particular immune response or disease being treated with the fusion protein (See column 12, line 63-65, in particular) and soluble receptor that function as a blocking agent is useful for treating lymphocyte mediated immunologically disease (See abstract, in particular). Hashimoto *et al* teach a polypeptide such as human and mouse CD79 α (Ig- α /mb-1) that is a B cell-associated antigen that forms heterodimer with CD79 β to become a B cell surface receptor (See page 287, column 2, page 288, Figures 1&2, in particular). Kooten *et al* teach that that the CD79 α (Ig- α /mb-1) and Ig- β (B29 or CD79 β) B cell receptor can be used for negative selection processes to eliminate B cells with specificity for autoantigens (See page 510, column 1, first paragraph, in particular). The '980 patent teaches that mutually exchange (self versus non-self) polypeptide can enhance the immunogenicity of self polypeptide and coupling of

Art Unit: 1644

one's own CH2-CH3 region to a non-species specific protein such as T cell epitope from *S japonicum*, one can circumvent tolerance to self polypeptide (autologous polypeptide) and give help to B-cells producing antibodies against a species specific antibodies (See column 5, lines 16-25, in particular). The recitation of second polypeptide is heterologous to the human subject is within the teachings of the '980 patent because the '980 patent teaches Fc domain swapping of self polypeptide for non-self (heterologous polypeptide).

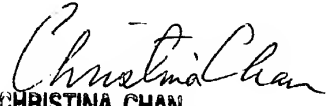
18. No claim is allowed.
19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.
20. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.

Patent Examiner

Technology Center 1600

February 24, 2003


CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600